

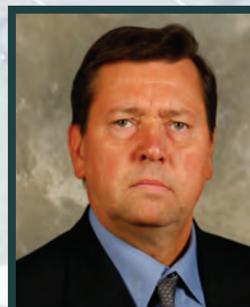
# Drug Development<sup>®</sup> & Delivery

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## Nanoparticulate Vaccine Formulations

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The science & business of drug development in specialty pharma, biotechnology, and drug delivery



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# PREFILLED SYRINGE STERILIZATION

## NO<sub>2</sub> Sterilization: A Flexible Solution for Prefilled Syringes

By: Evan Goulet, PhD, and Elizabeth Robbins

### INTRODUCTION

First patented 40 years ago, prefilled syringes have experienced tremendous growth alongside the increased development of large molecule drugs. The injectable drug delivery market is second in size only to that of oral medication, and prefilled syringes constitute one of the fastest growing segments of that market.<sup>1</sup> As opposed to their glass vial counterparts, prefilled syringes provide a cost-effective and user-friendly delivery system for a controlled dose of a biologic or drug product. With products that are intended for use in ophthalmic applications or administered in the sterile field of the operating room, it is often necessary to perform a sterilization or decontamination operation on the exterior surfaces of the syringe while in a sterile barrier package. With temperature-sensitive drugs or biologics, this can present challenges for manufacturers.

Today, the most commonly employed methods for sterilization are: steam, ethylene oxide (EO), and gamma radiation. These methods have served the market well for many years, but as drugs and delivery devices have advanced, some limitations have become apparent. Sterilization with traditional methods often requires exposure to elevated temperatures or damaging radiation, which may lead to degradation of the drug product or container closure materials. Additional concerns include leaching of sterilant

residuals from the stopper, the duration of the process, and the costs of sterilization.

Nitrogen dioxide (NO<sub>2</sub>) is a well-documented and researched gas. Sterilization with NO<sub>2</sub> gas can provide a solution to some of the limitations presented by existing options. It can also provide the process flexibility to manufacturers that will support continued innovation and growth in the prefilled syringe market. Noxilizer, Inc. designed the Noxilizer RTS 360™ Industrial NO<sub>2</sub> Sterilizer that provides surface sterilization of prefilled syringes with a range of material compatibility and low levels of residuals using its rapid, room-temperature process.

### CURRENT STERILIZATION OPTIONS FOR PREFILLED SYRINGES

Sterilization of prefilled syringes today is predominantly accomplished using steam, EO, or gamma radiation. While these methods are well established, their limitations could impede innovation and progress in the pharmaceutical and biotechnology industries. More than 60% of new drug products being developed today are biologics, such as protein therapies.<sup>1</sup> This rapid rise in biological drug development is expanding the market for new sterilization technologies that can overcome the limitations of current methods.

No single sterilization method will be compatible with every product on the market. Steam sterilization has been

around for more than a century and is well understood in both industrial and hospital settings. EO has a long track record with the broadest material compatibility, and gamma radiation offers a low-temperature option. Each of these methods has specific weaknesses with respect to sterilization of prefilled syringes. These weaknesses, discussed further, were the driving force behind the development of NO<sub>2</sub> sterilization.

At present, steam sterilization is the primary method employed for sterilization of glass prefilled syringes containing heat-stable products, such as saline. However, because it involves both very high temperature, typically 121°C, and pressure, it is not well suited to sensitive biologics and drugs. Further, more and more companies are looking to alternative plastic materials, like cyclic olefin copolymers (COCs), and fluoropolymer coatings to minimize any leaching or particulate interaction with the solubilized drug and patient.<sup>2</sup> Most of these new plastic materials cannot be exposed to high temperatures without experiencing degradation.

EO sterilization presents an alternative to steam sterilization for the external surfaces of prefilled syringes. However, EO also presents its own challenges. Although EO does not use the high temperatures of steam sterilization, it still requires temperatures in the range of 40°C to 60°C, and a relatively deep vacuum in order to

TABLE 1		
Safety-Related Property	Nitrogen Dioxide	Ethylene Oxide
Color	Reddish-Brown	Colorless
Odor Threshold	0.1 ppm	200-400 ppm
OSHA PEL	5 ppm	1 ppm
NFPA: Health	3	3
NFPA: Flammability	0	4
NFPA: Instability	0	3

**Comparison of Safety-Related Properties for NO<sub>2</sub> & EO**

achieve sterility. This can have an adverse effect on temperature-labile products, and the vacuum can cause unacceptable stopper movement due to pressure changes.

Drug manufacturers and researchers have long expressed concerns over the carcinogenic nature of residuals from the EO sterilization process.<sup>3</sup> The EO process can require lengthy aeration phases (9 to 17 days), often at elevated temperatures, to remove residuals from plastic syringes.<sup>4</sup> The lengthy aerations may compromise drug integrity or manufacturing efficiency. Another issue with EO is sterilant ingress, the diffusion of the sterilant past the container closure system into the product itself, which can lead to unacceptable levels of residuals within the drug product causing modifications to chemical structure and product activity.

EO sterilization also presents significant manufacturing and operator concerns. The cycle requires pre-conditioning and post-cycle aerations, which can lengthen the turnaround time considerably. Adding to this is the drawback of having the EO process performed off-

site, turnaround time can extend to 7 to 25 days, depending on the product. The EO process also involves health and safety concerns, with operators at risk of exposure to highly flammable, carcinogenic, and cytotoxic chemicals and residuals during routine operation and disposal.<sup>5</sup> Refer to Table 1 for a comparison of the safety-related properties of EO and NO<sub>2</sub>.

Another sterilization option is gamma radiation. Gamma does not require long aeration times and has relatively good materials and drug compatibility if a minimal radiation dose can be employed. This restriction can create cost concerns for smaller manufacturers as the entire process leading up to the final sterilization step must be done using aseptic processing in at least a Class 100 facility in order to be able to use a Bioburden Approach to process validation as opposed to the industry-accepted Overkill Approach. Additionally, gamma radiation is not ideal for aqueous drug products because it can produce toxic free radicals in the solution that can result in decreased drug activity. It can also break down preservatives used in many drug

**FIGURE 1**



solutions that are essential to maintaining stability and shelf-life of the product.

Gamma radiation has also been proven to interact with lubricants found in plastic syringes.<sup>6,7</sup> Lastly, the facility cost and mitigating the risk of exposing the operators to radiation must also be considered.<sup>8</sup>

Unique sterilization methods, such as Noxilizer's NO<sub>2</sub> sterilization process, offer a much-welcomed alternative to companies working to sterilize drugs delivered via prefilled syringes or delivery systems.

### NOXILIZER'S STERILIZATION TECHNOLOGY FOR PREFILLED SYRINGES

Noxilizer's advanced room-temperature sterilization process uses NO<sub>2</sub>, a well-researched gas, in combination with humidity to inactivate resistant microorganisms and deliver sterile product. The FDA recommends adding an adjunct process, or additional sterilization step, to "increase the level of sterility confidence"

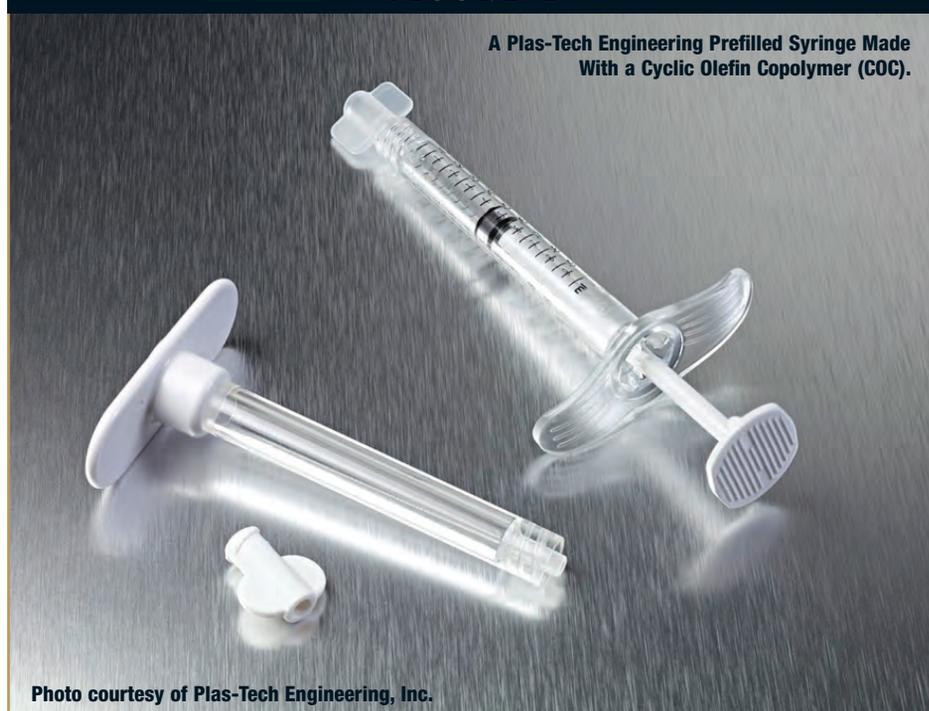
when aseptic processing is used in drug manufacturing.<sup>9</sup> This is especially true for products that are intended for use in ophthalmic applications or in the sterile field of the operating room. NO<sub>2</sub> gas is a surface sterilant that does not penetrate the container closure system and results in low surface residuals. The capability to sterilize at room temperature is fundamentally important because the rate of chemical reactions is approximately doubled for every 10°C rise in temperature. Maintaining

lower temperatures ensures that any reactions that might occur with the product, such as denaturation and agglomeration, are minimized.

NO<sub>2</sub> is a non-condensing gas, and as such, it can be an excellent sterilization choice for lumens, needles, and other challenging geometries in comparison to condensing vapor systems.<sup>10</sup> Coupled with the ability to sterilize with low humidity and temperature, this gives NO<sub>2</sub> a distinct advantage when considering sterilization of combination medical devices and surface sterilization of the final product.

Noxilizer's NO<sub>2</sub> technology is especially well suited to, and can be conveniently installed as, an adjunct process for products that require surface sterilization (Figure 1). By providing solutions to the challenges presented by steam, EO, and gamma sterilization, NO<sub>2</sub>

**FIGURE 2**



can help broaden the horizon for use of all types of prefilled syringes, including dual-chamber and combination devices, as the drug delivery system of the future.

NO<sub>2</sub> works as an oxidizer that inactivates microorganisms through degradation of DNA, providing a sterility assurance level (SAL) of 10<sup>-6</sup> at relatively low gas concentrations. Biological indicators for the NO<sub>2</sub> sterilization process consist of spores of *Geobacillus stearothermophilus*, which is the same organism used for steam sterilization.

A recent study, performed in the Noxilizer lab, demonstrated a 6-log reduction in the population of biological indicators placed next to the plunger rod in the barrels of water-filled COC syringes. The syringes, along with thermoplastic elastomer tip caps and stoppers, were provided by Plas-Tech Engineering, Inc. of Lake Geneva, WI (Figure 2). For the study, they were packaged in Tyvek-Mylar pouches. The exposure used in the study employed minimal vacuum (less than 1 psig) to deliver 10 mg/L NO<sub>2</sub> and 75% RH for a dwell time of 45 minutes. Including a 30-minute aeration phase, the total cycle time was 90 minutes.

A cycle that was 50% more aggressive in both concentration and exposure time was used to characterize sterilant ingress in the COC syringes. When tested via ion chromatography, water from the syringes exhibited residual nitrate levels that were

TABLE 2		
	Noxilizer RTS 360™	Typical EO System
Estimated Average Cycle Time	120 minutes	12-18 hours
Capacity	360 Liters	2200 Liters
Pre-conditioning	No	Yes
Estimated Aeration Time	60 minutes	9 days <sup>4</sup>
Relative Humidity	Low to High (30%-80%)	High (70%)
Vacuum	Minimal	Yes
Operating Temperature	Room Temperature	40°C-60°C
PFS Material Compatibility	Yes	Yes
Sterilant Ingress	Below WFI limit	Common Issue
Residuals	Low non-cytotoxic non-carcinogenic	Low cytotoxic carcinogenic
Operator & Environmentally Friendly	Yes	No
Manufacturing to Release Time	On-site, immediate release	Off-site, 7-24 day turnaround

**Comparison of NO<sub>2</sub> & EO for Prefilled Syringe (PFS) Sterilization**

below the limit of detection (2 µg/mL). When determined via a pH measurement method, the nitrate residuals were 0.002 ppm, which is 100 times below the Water for Injection (WFI) limit of 0.2 ppm stated in the European Pharmacopoeia.<sup>11</sup>

Noxilizer's demonstrated ability to sterilize the exterior surfaces of polymeric prefilled syringes using a rapid cycle, minimal vacuum, and a truly room temperature process suggests that NO<sub>2</sub> sterilization is an ideal solution for manufacturers of sensitive biopharmaceuticals. Table 2 provides a comparison of NO<sub>2</sub> sterilization with EO. In addition to the advantages outlined in Tables 1 and 2, the financial benefit of using NO<sub>2</sub> instead of EO could also be substantial (up to 40% to 60% cost savings). NO<sub>2</sub> sterilization equipment is significantly less expensive and does not

require extensive facility modifications to be installed. This would allow manufacturers currently using contract sterilization to move their sterilization process in-house, thereby reducing costs and turnaround times. NO<sub>2</sub> gas offers a faster and more compatible option to companies looking to manufacture their products in prefilled syringes.

The RTS 360™ can be easily installed in any manufacturing setting with a 240-VAC, single-phase connection. No other facility modifications or specialized equipment, such as an EO abator, are required. After exposure, the exhaust gases from the NO<sub>2</sub> sterilization process are passed through an on-board scrubber, which neutralizes the sterilant, rendering the exhaust safe for the operator and the environment. The spent scrubber material is a solid, landfill-safe material. This makes

**FIGURE 3**

**The Patented Noxilizer RTS 360™ Industrial NO<sub>2</sub> Sterilizer**



bringing sterilization in-house easy and safe, resulting in faster turnaround times.

For those manufacturers who would prefer to have sterilization done off-site, Noxilizer offers contract sterilization services in ISO 13485-certified facilities. Noxilizer's microbiology and materials science expertise is available to develop and validate processes specific to a customer's product needs.

### **ADDITIONAL APPLICATIONS OF NO<sub>2</sub> STERILIZATION IN THE SYRINGE MANUFACTURING PROCESS**

While NO<sub>2</sub> gas provides an excellent option for surface sterilization of the final prefilled syringe product, there are also clear benefits to integrating NO<sub>2</sub> sterilization into other steps of the prefilled syringe manufacturing process. With the same NO<sub>2</sub> technology, Noxilizer has

developed the NOX FLEX™ Rapid Biodecontamination System, which provides significant gains in cycle times versus current technologies. Noxilizer has also designed an in-line sterilization system that will allow manufacturers of syringe components to efficiently sterilize product without having to send truckloads of syringe tubs to EO contract sterilization facilities. A similar system can also be used to decontaminate the exterior surfaces of the syringe tubs prior to entering a filling isolator without the concern of shadowing that arises with e-beam. In a related area, Noxilizer has already completed a global supply agreement with Weiler Engineering, Inc. for an NO<sub>2</sub> decontamination system for their Blow-Fill-Seal aseptic filling equipment. ♦

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## BIOGRAPHIES



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